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Therapeutic Review
Short Acting Narcotics

Overview/Summary

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1] It is a subjective experience that is difficult to identify or quantify by any observer and is unique to the individual. The type of pain that one may experience is often described by its pathophysiological source. Somatic pain is due to activation of pain receptors in cutaneous or deep tissues. This type of pain is usually well localized and is described as sharp in nature. Visceral pain involves internal areas of the body, may be poorly localized, and described as an ache. Neuropathic pain is generally described as burning or electrical in nature. This type of pain is due to neuronal injury and may have a corresponding neurological deficit.[2] Understanding the type of pain and its source will play a role in choosing pain management therapies.

Successful pain management can be a difficult goal to attain. An individual's reaction to pain and response to pain management can be highly variable. Pain thresholds vary greatly between patients and responses to therapy will vary between persons and may vary within the same patient from day to day. Pain management can be multifaceted and may incorporate both pharmacological and non-pharmacological therapies. Successful pain management may require frequent reassessment of pain level and response to therapy with adjustments made accordingly.

Opioids have been a mainstay in the treatment of moderate to severe pain associated with a number of etiologies and opioids are commonly used in the postoperative and malignant pain settings. Although the routine use of opioids in nonmalignant pain is controversial, opioids are an acceptable alternative to other analgesic interventions that have been ineffective.[2]

Opioids produce their pharmacologic and adverse effects through binding to opioid receptors throughout the central nervous system and peripheral tissues. These agents may be classified by their ability to stimulate or block three types of opioid receptors: mu, kappa, and delta. The mu receptor is considered the prototypical opioid receptor. When stimulated, the mu receptor produces analgesia, euphoria, reduced gastrointestinal motility, respiratory depression, sedation, nausea, tolerance, and physical dependence. Kappa receptor stimulation produces analgesia, dysphoria, psychotomimetic effects, miosis, and respiratory depression. Stimulation of the delta opioid receptor produces analgesia without respiratory depression.[2]

Opioids may be administered via many routes. The general consensus is to use the least invasive, most cost-effective method of delivery before moving on to more invasive administrative techniques. Unlike other analgesic classes, opioids have well-accepted equianalgesic doses, which allows clinicians to convert between agents and between routes of administration. Additionally, pure opioid agonists do not have a ceiling effect as other analgesics do, therefore, additional analgesia may be obtained by increasing the opioid dose. Close monitoring after an opioid conversion or dosage change is required to evaluate the need for further dosage adjustments.[2]

Combination therapy has been widely used for the clinical management of acute pain; by combining 2 agents with different mechanisms of action, the combination therapy provides additive analgesic effects while reducing the risk of adverse effects. Additionally, combination therapies overcome the "ceiling

effects" of their individual components. Opioids are found in combination products along with aspirin, acetaminophen, ibuprofen, caffeine, and butalbital.[3]

In patients that experience chronic pain, it is recommended that once a stable short acting (immediate release) opioid dose is reached, the patient then be converted to a long-acting agent.[2] The long-acting opioid should be used on a scheduled basis, with as needed short-acting medications prescribed for breakthrough pain. The as needed dose should be approximately 15% to 50% of the total daily scheduled medication dose.[2] Patients who routinely require frequent breakthrough doses within a dosing interval may benefit from an increase in their scheduled medication. The goal is to maintain a constant level of pain relief with the scheduled medication, while only occasionally requiring the breakthrough medication.

Opioids are classified as controlled substances by the Food and Drug Administration (FDA) due to their known potential for abuse. However, it is important to recognize that tolerance and physical dependence are potential and common physiologic changes that occur in most patients who receive opioids for a sustained amount of time. Tolerance is defined as the need for increased dosage to produce the same effect or a reduced effect is observed with a constant dose. Physical dependence occurs when the body becomes accustomed to receiving opioids due to neuroadaption.[4] If the opioids are stopped or decreased abruptly, or if an antagonist is administered, the body will exhibit withdrawal symptoms. To avoid opioid withdrawal, the dose of opioids should be slowly tapered (25% reduction in dose every other day) upon drug discontinuation.[2] Psychological dependence, or addiction, indicates that the patient is taking the medication for reasons for their psychic effects and is characterized by compulsive use despite harm. This occurrence is not a characteristic of the drug class alone, but is a combined effect of biochemical, societal, and psychological factors affecting the patient.[4]

This review encompasses those agents referred to as short acting narcotics (opioid agonists). Long-acting narcotics, agonist-antagonist agents, and other therapeutic options for treating pain are covered in reviews found elsewhere. Agents included in this review are FDA scheduled II-IV, are self-administered and include both single entity and combination products.

Medications

Table 1. Medications Included Within Class Review*

Generic Name (Trade name)	Medication Class	Schedule	Generic Availability
Single Entity Products			
Codeine	Opioid agonist	II	✔
Hydromorphone (Dilaudid®)	Opioid agonist	II	✔
Meperidine (Demerol®)	Opioid agonist	II	✔
Morphine immediate release (IR) (Roxanol®)	Opioid agonist	II	✔
Oxycodone (Roxicodone®, Oxy IR®, OxyFast®, Oxydose®)	Opioid agonist	II	✔
Oxymorphone (Opana®)	Opioid agonist	II	-
Propoxyphene (Darvon®)	Opioid agonist	IV	✔
Propoxyphene napsylate (Darvon-N®)	Opioid agonist	IV	-
Combination Products			
Codeine/acetaminophen (APAP) (Capital w/ Codeine®, Vopac®, Tylenol w/ Codeine®)	Opioid agonist/non-salicylate analgesic	III	✔
Codeine/APAP/caffeine/butalbital (Fioricet w/ Codeine®)	Opioid agonist/non-salicylate analgesic/central nervous system stimulant/barbiturate	III	✔
Codeine/aspirin (ASA) (Empirin w/ Codeine®)	Opioid agonist/salicylate	III	✔

Generic Name (Trade name)	Medication Class	Schedule	Generic Availability
Codeine/ASA/caffeine/butalbital (Fiorinal w/ Codeine®)	Opioid agonist/salicylate/ barbiturate	III	✔
Dihydrocodeine/ASA/caffeine (Synalgos DC®)	Opioid agonist/salicylate/ central nervous system stimulant	III	-
Dihydrocodone/APAP/caffeine (Panlor DC®, Panlor SS®)	Opioid agonist/non-salicylate analgesic/central nervous system stimulant	III	✔
Hydrocodone/APAP (Vicodin®, Lortab®, Norco®, Anexsia®, Bancap-HC®, Co-Gesic®, Hydrocet®, Hycet®, Lorcet®, Maxidone®, Xodol®, Zamicet®, Zydone®)	Opioid agonist/non-salicylate analgesic	III	✔
Hydrocodone/ibuprofen (Vicoprofen®, Reprexain®)	Opioid agonist/non steroidal anti-inflammatory drug (NSAID)	III	✔
Oxycodone/APAP (Percocet®, Lynox®, Tylox®)	Opioid agonist/non-salicylate analgesic	II	✔
Oxycodone/ASA (Percodan®)	Opioid agonist/salicylate	II	✔
Oxycodone/ibuprofen (Combunox®)	Opioid agonist/NSAID	II	-
Propoxyphene/APAP (Balacet®, Darvocet A500®, Wygesic®)	Opioid agonist/non-salicylate analgesic	IV	✔
Propoxyphene/ASA/caffeine (Darvon-CPD®)	Opioid agonist/salicylate/central nervous system stimulant	IV	-
Propoxyphene napsylate/APAP (Darvocet N-100®, Darvocet N-50®)	Opioid agonist/non-salicylate analgesic	IV	✔

*The following agents are not included in this review: pentazocin (Talwin®), tramadol (Ultram®), Actiq®, Fentora®, butorphanol nasal spray and nalbuphine (Nubain®).

Indications

Overall, short acting narcotic medications are effective for the treatment of moderate-severe pain. The specific Food and Drug Administration-approved indications are summarized below in Table 2.

Table 2. Food and Drug Administration Approved Indications[5-21]

Generic Name	Mild to Moderate Pain	Moderate to Severe Pain	Other
Single Entity Product			
Codeine	✔		
Hydromorphone		✔	Post-operative pain
Meperidine		✔	
Morphine immediate release (IR)		✔	
Oxycodone		✔	
Oxymorphone		✔	
Propoxyphene	✔		
Propoxyphen napsylate	✔		
Combination Product			
Codeine/acetaminophen (APAP)	✔	✔	
Codeine/APAP/caffeine/butalbital			Tension Headache
Codeine/aspirin (ASA)	✔	✔	
Codeine/ASA/caffeine/butalbital			Tension Headache
Dihydrocodone/ASA/caffeine		✔	
Dihydrocodone/APAP/caffeine		✔	
Hydrocodone/APAP		✔	
Hydrocodone/ibuprofen			Short term management of

Generic Name	Mild to Moderate Pain	Moderate to Severe Pain	Other
			acute pain
Oxycodone/APAP		✔	
Oxycodone/ASA		✔	
Oxycodone/ibuprofen			Short term management of acute pain
Propoxyphene/APAP	✔		
Propoxyphene/ASA/caffeine	✔		
Propoxyphene napsylate/APAP	✔		

Pharmacokinetics

Table 3. Pharmacokinetics[5-21]

Generic Name (Trade name)	Bioavailability (%)	Onset (minutes)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products*					
Codeine	Readily absorbed	30-60	90 (3-16 unchanged)	Yes, (morphine, norcodeine)	2.5-3.5
Hydromorphone	62	30	Not reported	No	2.5
Meperidine	Variable	10-15	Not reported	Yes, (normeperidine, normeperidinic acid, meperidinic acid)	3.2-3.7 (metabo-lites: 24-48)
Morphine immediate release (IR)	25 (oral)	15-60 (oral)	90	Yes, (morphine-6-glucuronide)	2-3
Oxycodone	60-80	Not reported	Not reported	Yes (oxymorphone)	3.1-3.7
Oxymorphone	10	Not reported	40	Activity of metabolite (6-OH-oxymorphone) has not been evaluated	7-9
Propoxyphene and propoxyphene napsylate	Not reported	15-60	20-25 (1.5 unchanged)	Yes, (norpropoxyphene)	6-12
Additional Combination Product Ingredients					
Acetaminophen (APAP)	60-98	30	85	No	2-4
Aspirin (ASA)	Variable	20-30	Not reported	Yes, (salicylate)	4.7-9
Butalbital	Not reported	Not reported	59-88	Not reported	35
Caffeine	Not reported	15-45	70 (3 unchanged)	Yes, (Praxanthine, theobromine, theophylline)	4-5
Dihydrocodeine	21	30	35	No	3.4-4.5
Hydrocodone	80	30	Not reported	Yes, (hydromorphone)	3.8
Ibuprofen	71-92	15	45-79 as metabolites (1 unchanged)	No	2

* Single entity products may also be components of combination products included within this review.

Clinical Trials

Short acting narcotics have been studied in a number of clinical trials to evaluate and compare analgesic effects in the treatment of pain. A search for clinical trials evaluating the use of these agents in the treatment of various pains resulted in a substantial number of published articles. The studies included in this review are studies comparing the short acting narcotics with non-narcotic analgesics, non steroidal anti-inflammatory drugs, other short acting narcotics, and combination products. Patients included in these studies experienced a variety of pain including; dental pain, chronic pain, musculoskeletal pain, post-op pain, fractures, and cancer pain. Based on the collective results of these clinical trials, there is insufficient information to determine that any one short acting narcotic is more efficacious than another.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gimbel J[22] Oxymorphone IR 10, 20, or 30 mg vs oxycodone IR 10 mg vs placebo	DB, DR, MC, PC, PG, RCT Men and nonpregnant, nonlactating women, aged 18-75 years, receiving total hip or knee replacement surgery and scoring I to III on the ASA physical status classification system	N=300 First phase: 8 hours Second phase: 48 hours	Primary: TOTPAR, SPID and SPRID at 4,6, and 8 hours, safety Secondary: Not reported	Primary: Mean TOTPAR scores at 4, 6, and 8 hours for all doses of oxymorphone IR were statistically more efficacious compared to placebo ($P \leq 0.034$ and <0.001). Oxymorphone showed a statistically significant dose-response relationship in a regression model ($TOTPAR_8$) by using the arithmetic dose as the regressor (slope estimate, 0.184; $P<0.001$; 95% CI, 0.089 to 0.279) and reached an analgesic plateau at the 20-mg dose. Oxymorphone IR at 10, 20, and 30 mg was statistically more efficacious compared to placebo for SPID and SPRID at 4, 6, and 8 hours (*P* values 0.007-0.001). Although oxycodone IR was generally numerically greater compared to placebo, the differences were not significant for any efficacy measures (*P* values 0.333-0.195). The median time to meaningful pain relief was statistically significantly shorter in all of the oxymorphone IR groups (1 hour) than in the placebo group (1.5 hour; $P<0.05$). Fifty percent pain relief was achieved by 90.2% of patients in the oxymorphone IR 20 mg group ($P<0.001$), 82.4% of patients in the oxymorphone IR 10 mg group ($P=0.022$), 77.2% in the oxymorphone IR 30 mg group (*P* value not significant), and 69.2% in the oxycodone IR 10 mg group (*P* value not significant). The most frequent occurring adverse events in the oxymorphone IR groups were mild-to-moderate opioid side effects (i.e., nausea, vomiting, somnolence, and pruritus). During the single-dose phase, the incidence of adverse events was more frequent among the oxymorphone IR groups than in the oxycodone IR 10 mg group (39% to 50% versus 27%). In contrast, the incidence was somewhat more frequent in the oxycodone IR 10 mg group (82%) during the multiple-dose phase compared with the oxymorphone IR groups (61% to 71%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Palangio et al[23] Hydrocodone 7.5mg/ibuprofen 200 mg 2 tabs vs oxycodone 5 mg/APAP 325 mg 2 tablets vs placebo	DB, PC, PG, RCT Subjects ≥18 years of age with moderate to severe postoperative obstetric or gynecologic pain	N=180 8 hours	Primary: PR, TOTPAR, SPID scores, time to onset, adverse events Secondary: Not reported	Primary: Mean PR scores were similar for hydrocodone/ibuprofen and oxycodone/APAP at 0.5, 1, 1.5, 2, 2.5, 3, 4, and 7 hours and significantly greater for hydrocodone/ibuprofen than for oxycodone/APAP at 5 (P=0.003), 6 (P=0.043), and 8 (P 0.044) hours. Mean PR scores were significantly greater for hydrocodone/ibuprofen than for placebo at all measured times (P<0.001). Mean PR scores were significantly greater for oxycodone/APAP than for placebo at 0.5 (P<0.008), 1, 1.5, 2, 2.5, 3, and 4 (P<0.001), 5 (P=0.016) and 6 (P=0.031) hours. The mean TOTPAR was similar for hydrocodone/ibuprofen and oxycodone/APAP for the 0- to 3- and 0- to 4-hour intervals and significantly greater for hydrocodone/ibuprofen than for oxycodone/APAP at the 0- to 6- (P=0.043) and 0- to 8-hour (P=0.029) intervals. The mean SPID was similar for hydrocodone/ibuprofen and oxycodone/APAP for each interval. The mean SPID was significantly greater for hydrocodone/ibuprofen or oxycodone/APAP than for placebo for each interval (P<0.001). The median estimated time to onset of analgesia was similar for hydrocodone/ibuprofen (12.6 minutes) and oxycodone/APAP (15.4 minutes) and significantly shorter for either of these treatments than for placebo (29.5 minutes; P<0.001 and P=0.006, respectively). Eleven of 61 patients (18.0%) in the hydrocodone/ibuprofen group experienced adverse events, compared with 7 of 59 patients (11.9%) in the oxycodone/APAP group and 6 of 60 (10.0%) in the placebo groups. These findings were not statistically significant. Secondary: Not reported
Palangio et al[24] Hydrocodone 7.5	DB, MC, PG, RCT	N=469 4 weeks	Primary: Pain relief scores, number of daily	Primary: The overall mean pain relief scores for the entire study period were significantly greater in the HI2 group than either the HI1 group (P=0.003) or the CA group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/ibuprofen 200 mg (1 tablet) plus 1 tablet of placebo every 6-8 hours (HI1) vs hydrocodone 15 mg/ibuprofen 400 mg (2 tablets) every 6-8 hours (HI2) vs codeine 60 mg/APAP 600 mg (2 tablets) every 6-8 hours (CA)	Males and females ≥18 years of age with a chronic pain condition that required opioid or opioid-nonopioid combination analgesic therapy		doses of study medication, number of daily doses of supplemental analgesics, number of patients who discontinued therapy due to an unsatisfactory analgesic response, and global assessment scores Secondary: Not reported	(*P*<0.001). The weekly PR scores were significantly greater in the HI2 group than the HI1 group for weeks 1 (*P*<0.001), 2 (*P*<0.001), and 3 (*P*=0.008). The weekly mean PR scores were also significantly greater in the HI2 group than the CA group for weeks 1 (*P*<0.001), 2 (*P*<0.001), 3 (*P*<0.001) and 4 (*P*=0.007), and end point (*P*=0.003). The overall mean number of daily doses of supplemental analgesics was significantly less in the HI2 drop than either the HI1 group (*P*=0.21) or the CA group (*P*=0.01). There were no significant differences in the overall weekly mean number of daily doses of supplemental analgesics between the HI1 group and the CA group. The number of patients who discontinued treatment due to an unsatisfactory analgesic response was significantly less in the HI2 group (2/153; 1.3%) than in the CA group (12/160; 7.5%; *P*=0.08). There were no significant differences in the number of patients who discontinued treatment due to an unsatisfactory analgesic response between the HI1 group (8/156; 5.1%) and either the HI2 group or the CA group. The weekly mean global assessment scores were significantly greater in the HI2 group than the HI1 group for weeks 1 (*P*=0.018), 2 (*P*=0.005), and 4 (*P*=0.013). The weekly mean global assessment scores were significantly greater in the HI2 group than the CA group for weeks 1 (*P*<0.001), 2 (*P*<0.001), 3 (*P*=0.009), and 4 (*P*=0.023), and end point (*P*=0.016). There were no significant differences in the weekly mean global assessment scores between the HI1 group and the CA group. Secondary: Not reported
Clark et al[25] APAP 15 mg/kg	RCT Children 6-17 years of age	N=336 120 minutes	Primary: Change in pain from baseline to 60 minutes after	Primary: At 60 minutes, patients in the ibuprofen group had significantly greater improvement in pain score than those in the codeine and APAP groups (*P*<0.001). There was no significant difference in the change in pain score between the codeine and APAP

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ibuprofen 10 mg/kg vs codeine 1 mg/kg	presenting to the emergency department with pain from a musculoskeletal injury occurring in the preceding 48 hours		treatment as measured by a VAS Secondary: Change in VAS from baseline at 30, 90, and 120 minutes, requirement for additional analgesia, and the number of patients achieving a VAS<30 mm at 60 and 120 minutes	groups at any time period. Secondary: At 30 minutes there was no significant difference in change in pain score among the 3 groups. At 60 minutes, more patients in the ibuprofen group achieved adequate analgesia (as defined by a VAS<30 mm) than the other 2 groups. There was no statistical difference between the codeine and APAP groups. Over the course of the trial, there was no significant difference in the number of patients requiring additional analgesic (22.2% in the codeine group, 15.6% in the APAP group, and 14.3% in the ibuprofen group; *P*=0.32).
Simmons et al[26] Naproxen sodium 275 mg TID vs dextropropoxyphene 32.5 mg/APAP 325 mg, 2 tabs TID	PG, RCT, SB Males and females who had recently suffered acute musculo-skeletal disorders or acute traumatic sports injuries	N=184 7-14 days	Primary: Severity of pain, tenderness, swelling and limitation of movement, side effects Secondary: Not reported	Primary: Naproxen sodium was significantly better than dextropropoxyphene/APAP in pain at the day 7 assessment (*P*<0.05). For those patients who carried on for 14 days of treatment, the total symptom score was significantly different in favor of naproxen (*P*<0.05). There were no significant differences between the two treatment groups at day 7 and the day 14 follow-up for scores of tenderness, swelling, and limitations of movement. The majority of the side effects in the naproxen sodium group were related to the gastrointestinal tract (13 side effects reported) while the side effects in the dextropropoxyphene/APAP group were related to the central nervous system (31side effects reported). Secondary: Not reported
Rodriguez et al[27] Codeine 30 mg/APAP 500 mg (CA) every 4	DB, PG, PRO, RCT Subjects aged	N=121 23 days	Primary: Proportion of patients who achieved pain	Primary: Overall, 39/59 (66%) patients who received CA and 44/62 (71%) patients who used HA experienced pain relief (*P*=0.69).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hours vs hydrocodone 5 mg/APAP 500 mg (HA) every 4 hours	≥18 years of age with chronic moderate to severe cancer-related pain		relief Secondary: Proportion of patients in whom pain was decreased, adverse events	Of patients who received CA 34 (58%) experienced pain relief at the initial dosage and 5 (8%) responded to the double dosage. Twenty (34%) did not experience any pain relief with CA. HA was associated with mild pain intensity in 35 (56%) of patients at the starting dosage. An additional 9 (15%) patients responded to the double dosage and the remaining 18 (29%) patients did not experience any pain relief. The differences in pain relief were not significant between the groups. Secondary: Mean pain intensity decreased to a similar extent in the 2 treatment groups. The most common adverse events in the CA and HA groups were constipation (21 [36%] and 18 [29%], respectively), dizziness (14 [24%] and 12 [19%]), vomiting (14 [24%] and 10 [16%]), and dry mouth (9 [15%] and 11 [18%]). None of the differences between the 2 groups were statistically significant.
Marco et al[28] Oxycodone 5 mg/APAP as a combination liquid formulation vs hydrocodone 5 mg/ APAP as a combination liquid formulation	DB, PRO, RCT Emergency department patients over the age of 12 with fractures and severe pain, with pain scores ≥5 on a 0-10 scale	N=73 60 minutes	Primary: Pain score (verbal numeric rating scale) at 30 and 60 minutes Secondary: Presence and severity of side effects	Primary: Patients in both groups had pain relief from baseline to 30 minutes (oxycodone mean change 3.7; 95% CI, 2.9 to 4.6; hydrocodone mean change 2.5; 95% CI, 1.7 to 3.3) and from baseline to 60 minutes (oxycodone mean change 4.4; 95% CI, 3.2 to 5.6; hydrocodone mean change 3.0; 95% CI, 2.1 to 3.9). There was no difference in pain identified between the patients treated with oxycodone and hydrocodone at 30 minutes (mean difference between groups -0.6; 95% CI, -1.8 to 0.5) or at 60 minutes (mean difference -0.5; 95% CI, -2.0 to 1.0). Secondary: There was no difference between the groups in nausea, vomiting, itching, or drowsiness; however the hydrocodone patients had a higher incidence of subsequent constipation (oxycodone 0%, hydrocodone 21%, difference in proportions 21%; 95% CI, 3% to 39%).
Litkowski et al[3] Oxycodone 5 mg/ ibuprofen 400 mg	AC, MC, PC, PG, RCT Men or women	N=249 6 hours	Primary: Total pain relief through 6 hours after dosing	Primary: The combination of oxycodone/ibuprofen provided higher pain relief values than any of the other combinations tested or placebo. TOTPAR$_6$ scores were significantly better for each combination treatment compared with placebo (P<0.001). The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs oxycodone 5 mg/APAP 325 mg vs hydrocodone 7.5 mg/ APAP 500 mg vs placebo	aged ≥12 years of age who were scheduled to undergo complete removal of ≥2 ipsilateral, partially or completely impacted third molars		($TOTPAR_6$), sum of pain intensity differences through 6 hours ($SPID_6$), and adverse events Secondary: $SPID_3$,$TOTPAR_3$, peak pain relief, peak PID, time to onset of pain relief, time to use of rescue medication, proportion of patients reporting pain half gone, and the patient's global evaluation	combination of oxycodone/ibuprofen was associated with a significantly higher $TOTPAR_6$ score compared with oxycodone/APAP, hydrocodone/APAP, and placebo (mean [SD], 14.98 [5.37], 9.53 [6.77], 8.36 [6.68], and 5.05 [6.90], respectively; all, $P<0.001$). The results for $SPID_6$ were similar, with oxycodone/ibuprofen associated with significantly higher values compared with oxycodone/APAP, hydrocodone/APAP, and placebo (7.78 [4.11], 3.58 [4.64], 3.32 [4.73], and 0.69 [4.85]; all $P<0.001$). Both oxycodone/APAP and hydrocodone/APAP were associated with significantly higher $SPID_6$ scores compared with placebo ($P<0.001$ and $P=0.002$, respectively). The combination of oxycodone/ibuprofen was well tolerated, as evidenced by an overall rate of patients experiencing ≥1 adverse event that was similar to that for placebo (11.3% [7/62] and 11.1% [7/63], respectively). Rates in the groups receiving oxycodone/APAP and hydrocodone/APAP (27.9% [17/61] and 25.4% [16/63], respectively) were >2-fold higher. Secondary: For $TOTPAR_3$, $SPID_3$, peak pain relief, pain half gone, and the patient's global assessment, oxycodone/ibuprofen was associated with significantly better scores compared with oxycodone/APAP, hydrocodone/APAP, and placebo (all, $P<0.001$). Peak SPID scores were also significantly higher for oxycodone/ibuprofen compared with oxycodone/APAP ($P=0.006$). Compared with placebo, oxycodone/APAP and hydrocodone/APAP also were significantly better in terms of $TOTPAR_3$, $SPID_3$, the patient's global assessment (all, $P<0.001$), and peak pain relief ($P<0.001$ and $P=0.002$, respectively). The median time to the onset of pain relief was significantly shorter for oxycodone/ ibuprofen compared with hydrocodone/APAP ($P=0.002$) and placebo ($P<0.001$). Both oxycodone/APAP and hydrocodone/APAP were associated with significantly shorter median times to the onset of pain relief compared with placebo ($P<0.001$ and $P=0.002$, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Macleod et al[29] Codeine 30 mg/APAP 1,000 mg as a single tablet vs APAP 1,000 mg	DB, PG, PRO, RCT Subjects ≥17 undergoing surgical removal of impacted third molars	N=82 12 hours	Primary: Comparative pain management, adverse effects Secondary: Not reported	Primary: The average increase in pain intensity over 12 hours was significantly less in patients receiving codeine/APAP than in those receiving APAP alone (*P*=0.03). Escape analgesia (ibuprofen 200 mg) was used by 24 (62%) patients receiving codeine/APAP and 30 (75%) of those receiving APAP alone, a difference that was not statistically significant. A comparison of the adverse event profiles of the two medications showed that only 7 (18%) patients receiving codeine/APAP and 5 (13%) patients receiving APAP alone experienced an adverse event, a difference not statistically significant. Secondary: Not reported
Joshi et al[30] Ibuprofen 600 mg 1 hour before pre-op vs diclofenac 100 mg 1 hour pre-op vs codeine 60 mg/APAP 1,000 mg 1 hour pre-op vs placebo	DB, PC, RCT Men and women aged 18-44 who were to have third molar teeth removed under general anaesthesia	N=119 24 hours	Primary: Efficacy of pre-emptive dosing of pain medication pre-op as measured by pain (VAS) at 15 and 30 minutes, and (VRS) 1 hour and 3 hours post-op Secondary: Not reported	Primary: Median VAS scores decreased after 30 minutes post-op. There was no significant difference among the four groups. Verbal rating pain scores showed that at 3 hours, 17 patients (14%) had moderate pain not controlled by pain medication and 3 patients (3%) had severe pain. By 24 hours, 68 patients (57%) reported no pain, 24 (20%) had mild pain, 26 (22%) had moderate pain, and 1 patient had moderate pain not controlled by pain medications. There were no significant differences in total pain and pain intensity scores among the four groups. There was a significant difference between the placebo and diclofenac groups in regard to time to first requirement for postoperative analgesics (*P*≤0.009). When the pre-emptive and post-op analgesics were not sufficient to control pain, APAP 500 mg was available as rescue analgesia. Ninety-nine patients (83%) did not require rescue medication and of the 20 patients who requested analgesia, the proportion in each group was not dissimilar. There were no significant differences among the groups with respect to adverse events at 6 or 24 hours. Adverse events reported 6 hours post-op included nausea (19%), vomiting (7%), headaches (13%), gastrointestinal discomfort (12%), dizziness

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(24%) and other discomforts (29%). Secondary: Not reported

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DR=dose-ranging, MC=multicenter, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, SD=standard deviation
Miscellaneous abbreviations: APAP=acetaminophen, ASA=American Society of Anesthesiologists, IR=immediate release, IM=intramuscular, PR=pain relief, SPID=sum of pain intensity differences, SPRID=sum of combined pain relief and pain intensity differences, TID=three times a day, TOTPAR=total pain relief, VAS=visual analog scale, VRS=verbal rating scale.

Special Populations

Table 5. Special Populations[5-21]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products*					
Codeine	Use with caution in the elderly. Safe dosage has not been established in children below the age of 3.	Dosage should be reduced to 75% of the usual dose for patients with moderate renal failure or to 50% of the usual dose for patients with severe renal failure.	Use caution in with severe hepatic impairment.	C	Yes (% not reported)
Hydromorphone	Dose selection for elderly should be cautious and the initial dose should be reduced due to the greater frequency of decreased hepatic, renal, or cardiac functions. Safety and effectiveness in children have not been established.	Initial dose should be reduced for those with severe renal impairment.	Initial dose should be reduced for those with severe hepatic impairment.	C	Not reported
Meperidine	Geriatric patients have a slower elimination rate compared to young patients and may be more susceptible to the effects of meperidine; a reduction in total daily dose may be required. Meperidine has a slower elimination rate in neonates and young infants compared to older children and adults;	Use with caution as accumulation of meperidine and/or its metabolite, nor-meperridine, can occur.	Use with caution as accumulation of meperidine and/or its metabolite, nor-meperridine, can occur.	C	Yes (% not reported)

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	use with caution in neonates and young infants.				
Morphine immediate release (IR)	Use in the elderly population should be done with caution. Safety and effectiveness in pediatric patients have not been established.	Dosage should be reduced to 75% of the usual dose for patients with moderate renal failure or to 50% of the usual dose for patients with severe renal failure.	Avoid use in patients with severe hepatic impairment.	C	Yes (% not reported)
Oxycodone	Use in the elderly population should be done with caution.	Use with caution in patients with severe renal impairment.	Use with caution in patients with severe hepatic impairment.	B	Yes (% not reported)
Oxymorphone	Should be used with caution in elderly patients. Plasma levels of oxymorphone are about 40% higher in elderly (≥65 years of age) than in younger subjects. Safety and effectiveness pediatric patients below the age of 18 years have not been established.	There are 57% and 65% increases in bioavailability in patients with moderate to severe renal impairment. Administer cautiously at reduced doses in patients with creatinine clearance less than 50 mL/min.	Contraindicated in patients with moderate and severe hepatic dysfunction. Patients with mild hepatic impairment should be started with the lowest dose and titrated slowly while carefully monitoring side effects.	C	Unknown
Propoxyphene and propoxyphene napsylate	Prolonged dosage intervals may be considered in the elderly as the metabolism of propoxyphene may be reduced in this patient population. Safety and effectiveness in pediatric patients	Should be used cautiously and a reduced dose considered in patients with renal failure.	Cases of hepatotoxicity have been reported. Should be avoided in patients with hepatic insufficiency.	C	Yes (% not reported)

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	have not been established.				
Additional Combination Product Ingredients					
Acetaminophen (APAP)	Despite reports of a prolonged half-life in elderly patients, no specific dosage adjustment is necessary. The dosage is based on weight in pediatric patients.	Increase the dosing interval to every 4 hours in patients with mild renal failure, every 6 hours in patients with moderate renal failure, and every 8 hours in patients with severe renal failure.	Can be safely administered in therapeutic doses in the presence of chronic stable hepatic disease.	B	Yes (% not reported)
Aspirin (ASA)	No dosage adjustments are required for elderly patients. Use in children or adolescents for the treatment of fever and muscle ache associated with viral illness should be avoided due to the possible association with Reye's Syndrome. Use should also be avoided in neonates and children less than one year of age.	Patients with severe renal failure should avoid aspirin.	Should be avoided in severe hepatic insufficiency.	D	Yes (% not reported)
Butalbital	Not reported	Not reported	Not reported	C	Yes (% not reported)
Caffeine	Dosage adjustments not required.	Not reported	Requirement for dosage adjustment in hepatic impairment is unknown.	B	Yes (% not reported)
Dihydrocodeine	Initial dosing in the elderly should be	Use with caution and at	Use with caution in	C	Yes (% not

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	cautious. Safety and efficacy in pediatric patients have not been established.	reduced doses in the presence of impaired renal function.	patients with hepatic dysfunction.		reported)
Hydrocodone	The elderly should be started at the low end of the dosing range and titrated to effect. Caution should be exhibited due to the population's predisposition for hepatic and renal insufficiency. Can cause confusion and increased sedation in the geriatric population.	Use caution in those with severe renal impairment.	Use caution in those with severe hepatic insufficiency.	C	Unknown
Ibuprofen	Dosage adjustment not required in the elderly. The dosing in pediatric patients is weight based.	No dosage adjustment is recommended for patients with renal dysfunction or failure.	Data suggests dosage adjustment in severe hepatic insufficiency is not required.	D	No

* Single entity products may also be components of combination products included within this review.

Adverse Drug Events[5-21]

The adverse drug events for the short acting narcotics are similar to each other and represent the pharmacologic effects of the drug class. The most serious and most feared opioid-induced adverse reaction is respiratory depression. Clinically significant respiratory depression is rare when opioids are given to patients who are experiencing acute pain. Additionally, patients receiving opioids chronically rarely experience this effect since tolerance to respiratory depression develops.

The most frequently observed adverse effects include nausea and vomiting, sedation, constipation, dizziness, and lightheadedness. These adverse effects typically occur early in therapy or immediately after a dosage increase. Over time these adverse events tend to subside as tolerance develops. However, constipation is the one exception as unlike other opioid induced adverse effects tolerance to constipation does not develop.

Other adverse drug events commonly seen with the short acting narcotics are:
Cardiovascular System: bradycardia, faintness, flushing of the face, palpitations, syncope
Central Nervous System: agitation, convulsions, depression, disorientation, dreams, dysphoria, euphoria, headache, insomnia, muscle rigidity, nervousness, transient hallucinations, tremor, uncoordinated muscle movements, visual disturbances, and weakness

Dermatologic: edema, hemorrhagic urticaria, pruritus, rash, sweating, urticaria
Gastrointestinal: anorexia, biliary tract spasm, dry mouth
Genitourinary System: anti-diuretic effect, reduced libido and/or potency, urinary retention,.
Respiratory System: bronchospasm

Contraindications / Precautions[5-21]
The short acting narcotics should not be administered to patients with known hypersensitivity to any component of the product.

Short acting narcotics are contraindicated in patients with significant respiratory depression. They should be used in caution in patients with acute asthma, chronic obstructive pulmonary disorder, or preexisting respiratory impairment. Additionally, the respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid may be markedly exaggerated in the presence of head injury, intracranial lesions, or a pre-existing increase in intracranial pressure.

Opioid analgesics may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone.

Ibuprofen, a non steroidal anti-inflammatory (NSAID) has been associated with cardiovascular and gastrointestinal risks which has led to the black box listed below. The short acting narcotics have also been assigned black box warnings for various safety concerns and are outlined below. Long acting formulations of narcotics have additional back box warnings which are not outlined in this review.

Black Box Warning for Ibuprofen Containing Agents[21]

WARNING
Cardiovascular Risk • NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. **Gastrointestinal Risk** • NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Black Box Warning for Propoxyphene Containing Agents[5,14]

WARNING
Fatalities: • Do not prescribe propoxyphene for patients who are suicidal or addiction prone. • Prescribe propoxyphene with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess. • Tell patients not to exceed the recommended dose and to limit alcohol intake. Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants (including alcohol), are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, in approximately 20% of fatal cases, death occurred within the first hour (5% within 15 minutes). Propoxyphene should not be taken in higher doses than those recommended by the health care provider. Judicious prescribing of propoxyphene is essential for safety. Consider nonopioid analgesics for depressed or suicidal patients. Caution patients about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of added CNS depressant effects, cautiously prescribe with concomitant sedatives, tranquilizers, muscle

WARNING
relaxants, antidepressants, or other CNS-depressant drugs. Advise patients of the additive depressant effects of these combinations. Many propoxyphene-related deaths have occurred in patients with histories of emotional disturbances, suicidal ideation or attempts, or misuse of tranquilizers, alcohol, and other CNS-active drugs. Deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Do not exceed the recommended dosage

Black Box Warning for Hydromorphone Injection[5,7]

WARNING
High-potency hydromorphone injection is a highly concentrated solution of hydromorphone, a potent schedule II controlled opioid agonist intended for use in opioid-tolerant patients. Do not confuse high-potency hydromorphone injection with standard parenteral formulations of hydromorphone or other opioids. Overdose and death could result.[1 2]

Black Box Warning for Morphine Injection[5,10]

WARNING
Astramorph PF, Infumorph, Duramorph: Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose. **Infumorph:** Infumorph is not recommended for single-dose intravenous (IV), intramuscular (IM), or subcutaneous administration because of the very large amount of morphine in the ampul and the associated risk of overdosage.

Drug Interactions

Drug interactions associated with the single entity short acting narcotics and other single entity products that are components of combination short acting narcotic products are outlined below in Table 6.

Table 6: Drug Interactions[5-21]

Generic Name	Interacting Medication or Disease	Potential Result
Codeine, Hydrocodone, Hydromorphone, Meperidine, Morphine, Oxycodone, Oxymorphone	Central nervous system depressants	May produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur.
Butalbital, Hydrocodone, Meperidine, Morphine, Oxycodone	Monoamine oxidase inhibitors (MAOIs)	MAOIs have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion, and significant depression of respiration or coma. Use within 14 days of stopping MAOI treatment is not recommended.
Hydrocodone, Hydromorphone, Morphine, Oxycodone	Neuromuscular blocking agents	Opioid analgesics may enhance the action of neuromuscular blocking agents and may produce an increased degree of respiratory depression.
Hydrocodone, Oxycodone, Oxymorphone	Anticholinergics	Concurrent use may produce increased urinary retention and/or severe constipation, which may lead to paralytic ileus.

Generic Name	Interacting Medication or Disease	Potential Result
Hydrocodone, Oxycodone, Oxymorphone	Mixed agonist/ antagonist opioid	Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.
Ibuprofen, Aspirin (ASA)	Angiotensin converting enzyme (ACE)-inhibitors	Ibuprofen may diminish the antihypertensive effect of the ACE-inhibitor.
Ibuprofen, ASA	Warfarin, Heparin	Effects on gastrointestinal bleeding are synergistic.
Propoxyphene, Acetaminophen (APAP)	Beta-blockers (Propranolol)	Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of APAP. The pharmacologic effects of APAP may be increased.
APAP	Alcohol, ethyl	Hepatotoxicity has occurred in chronic alcoholics following various dose levels of APAP.
APAP	Lamotrigine	Serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effects.
APAP	Loop diuretics	The effects of the loop diuretic may be decreased because APAP may decrease renal prostaglandin excretion and decrease plasma rennin activity.
APAP	Oral contraceptives	Increase in glucuronidation resulting in increased plasma clearance and a decreased half-life of APAP.
APAP	Probenecid	Probenecid may increase the therapeutic effectiveness of APAP.
APAP	Zidovudine	The pharmacologic effects of zidovudine may be decreased because of its enhanced non-hepatic or renal clearance.
ASA	Acetazolamide	Concurrent use can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.
ASA	Methotrexate	ASA may enhance the serious side effects and toxicity of methotrexate due to displacement from its plasma protein binding sites and/or reduced renal clearance.
Ibuprofen	Lithium	Elevation of plasma lithium levels and a reduction in renal lithium clearance may occur with concomitant use.
Meperidine	Acyclovir	Increased serum concentration of Meperidine may occur with concomitant use..
Morphine	Rifampin	Concurrent use of morphine and rifampin may result in loss of morphine efficacy.
Oxycodone	CYP2D6 inhibitors	Metabolism of oxycodone may be inhibited with concomitant use..
Oxymorphone	Cimetidine	Central nervous system side effects (confusion, disorientation, respiratory depression, apnea, seizures) have been reported with concomitant use.
Propoxyphene	Carbamaz-apine	Concurrent use of may result in an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma).
Propoxyphene	Cigarette smoke	Concurrent use may result in decreased propoxyphene concentrations.

Dosage and Administration

Table 7. Dosing and Administration[5-21]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Codeine	Intramuscular (IM)/oral/ subcutaneous (SC): 15 to 60 mg every 4 to 6 hours as needed; maximum, 360 mg/day	Oral: 0.5 to 1 mg/kg every 4 to 6 hours as needed; maximum, 60 mg/dose	Injection (phosphate): 30 mg 60 mg Solution (phosphate): 15 mg/5 mL Tablet (sulfate): 15 mg 30 mg 60 mg
Hydromorphone	IM/SC: initial, 0.8 to 1 mg every 4-6 hours as needed; usual range, 1 to 2 mg every 3-6 hours as needed Oral: initial, 2 to 4 mg every 3-4 hours as needed; usual range, 2 to 8 mg every 3-4 hours as needed Rectal: 3 to 6 mg every 3-8 hours as needed	Safety and efficacy in children have not been established.	Ampoules: 1 mg/mL 2 mg/mL 4 mg/mL 10 mg/mL Liquid: 1 mg/mL Suppository: 3 mg Tablet: 2 mg 4 mg 8 mg
Meperidine	IM/SC/oral: 25 to 150 mg every 3-4 hours as needed	Oral: 0.5 to 0.8 mg/lb up to the adult dose, every 3-4 hours as needed	Injection: 10 mg/mL 25 mg/mL 50 mg/mL 75 mg/mL 100 mg/mL Syrup: 50 mg/5 mL Tablet: 50 mg 100 mg
Morphine	IM/SC: 2.5 to 20 mg every 2-6 hours as needed Oral: 5 to 30 mg every 4 hours as needed Rectal: 10 to 30 mg every 4 hours as needed	Safety and efficacy in pediatric patients have not been established.	Injection: 0.5 mg/mL 1 mg/mL 2 mg/mL 4 mg/mL 5 mg/mL 8 mg/mL 10 mg/mL 15 mg/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
			25 mg/mL 50 mg/mL Solution: 10 mg/5 mL 20 mg/5 mL 20 mg/mL Suppository: 5 mg 10 mg 20 mg 30 mg Tablet: 15 mg 30 mg
Oxycodone	Oral: 5 to 30 mg every 6 hours as needed	Safety and efficacy in pediatric patients have not been established.	Capsules: 5 mg Solution: 5 mg/5 mL 20 mg/mL Tablets: 5 mg 10 mg 15 mg 20 mg 30 mg
Oxymorphone	IM: 1-1.5 mg every 4-6 hours as needed Oral: 5 to 20 mg every 4-6 hours as needed; maximum, 20 mg every 4-6 hours	Safety and efficacy in pediatric patients have not been established.	Ampoule: 1 mg/mL Tablet: 5 mg 10 mg
Propoxyphene	Oral: 65 mg every 4 hours as needed; maximum, 390 mg/day	Safety and efficacy in pediatric patients have not been established.	Capsule: 65 mg
Propoxyphene napsylate	Oral: 100 mg every 4 hours as needed; maximum, 600 mg/day	Safety and efficacy in pediatric patients have not been established.	Tablet: 100 mg
Combination Products			
Codeine/ acetaminophen (APAP)	Oral: 15 to 60 mg (of codeine) every 4 hours as needed; maximum, 360 mg of codeine daily and 4,000 mg APAP daily	Safety not established in children less than 3 years of age. Oral: 0.5 mg/kg (of codeine) every 3-4 hours as needed	Suspension: 12 mg/120 mg per 5 mL Tablet: 15 mg/300 mg 30 mg/300 mg 60 mg/300 mg 30 mg/650 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Codeine/APAP/ caffeine/butalbital	Oral: 1 or 2 capsules every 4 hours as needed; maximum, 6 capsules daily	Safety and efficacy in pediatric patients have not been established.	Capsule: 30 mg/325 mg/40 mg/50 mg
Codeine/aspirin (ASA)	Oral: up to 60 mg (of codeine) every 4 hours as needed	Safety and efficacy in pediatric patients have not been established.	Tablet: 30 mg/325 mg 60 mg/325 mg
Codeine/ASA/ caffeine/butalbital	Oral: 1 or 2 capsules every 4 hours as needed; maximum, 6 capsules daily	Safety and efficacy in pediatric patients have not been established.	Capsule: 30 mg/325 mg/40 mg/30 mg
Dihydrocodone/ ASA/caffeine	Oral: 2 capsules every 4 hours as needed	Safety and efficacy in pediatric patients have not been established.	Capsule: 16 mg/356.4 mg/30 mg
Dihydrocodone/ APAP/caffeine	Oral: 2 capsules every 4 hours as needed; maximum, 10 capsules/day	Safety and efficacy in pediatric patients have not been established.	Capsule: 16 mg/356.4 mg/30 mg Tablet: 32 mg/712.8 mg/60 mg
Hydrocodone/ APAP	Capsule, tablet: 1 or 2 every 4-6 hours as needed; maximum, 6 to 8/day (60 mg hydrocodone, 4 g APAP) Solution: 5-15 mL every 4-6 hours as needed; maximum, 90 mL daily	2-13 years old: 0.135 mg/kg hydrocodone and 9 mg/kg APAP every 4-6 hours as needed; maximum, 6 doses/day	Capsule: 5 mg/500 mg Solution: 2.5 mg/167mg per 5 mL 7.5 mg/500 mg per 15 mL 10 mg/325 mg per 15 mL Tablet: 5 mg/325 mg 7.5 mg/325 mg 10 mg/325 mg 5 mg/400 mg 7.5 mg/400 mg 10 mg/400 mg 2.5 mg/500 mg 5 mg/500 mg 7.5 mg/500 mg 10 mg/500 mg 7.5 mg/650 mg 10 mg/650 mg 10 mg/660 mg 7.5 mg/750 mg 10 mg/750 mg
Hydrocodone/ ibuprofen	Oral: 1 tablet every 4 to 6 hours as needed; maximum, 5 tablets/day for 10 days	Safety and efficacy in pediatric patients below the age of 16 have not been established.	Tablet: 7.5 mg/200 mg
Oxycodone/ APAP	Oral: 2.5 to 10 mg (of oxycodone) every 4-6 hours as needed; initial dose based on oxycodone content; maximum dose based on APAP content	Safety and efficacy in pediatric patients have not been established.	Tablet: 2.5 mg/325 mg 5 mg/325 mg 7.5 mg/500 mg 10 mg/325 mg 10 mg/650 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Oxycodone/ASA	Oral: 1 tablet every 6 hours as needed	Safety and efficacy in pediatric patients have not been established.	Tablet: 4.8355 mg/325 mg
Oxycodone/ ibuprofen	Oral: 1 tablet every 6 hours as needed; maximum, 4 tablets/day for 7 days	Safety and efficacy in pediatric patients below the age of 14 have not been established.	Capsules: 5 mg/400 mg
Propoxyphene/ APAP	Oral: 1 capsule every 4 hours as needed; maximum 6 capsules/day	Safety and efficacy in pediatric patients have not been established.	Capsule: 65 mg/650 mg
Propoxyphene ASA/caffeine	Oral: 1 capsule every 4 hours as needed; maximum 6 capsules/day	Safety and efficacy in pediatric patients have not been established.	Capsule: 65 mg/389 mg/32.4 mg
Propoxyphene napsylate/APAP	Oral: 1 tablet every 4 hours as needed; maximum 6 tablets/day	Safety and efficacy in children under 12 years of age have not been established.	Tablet: 50 mg/325 mg 100 mg/325 mg 100 mg/500 mg 100 mg/650 mg

Other Key Facts

During the course of pain management the process of converting from one opioid to an equivalent dose of another, or changing the route of administration, can be done using morphine as a reference. The following eight steps can be utilized when a change is appropriate:[32]

Step 1: Determine the total 24-hour dose of the currently prescribed analgesic.
Step 2: Convert the currently prescribed opioid to the equivalent morphine dose.
Step 3: Convert the morphine dose to an equivalent dose of the new opioid using the same route of administration using the following conversions:

- Consider reducing the dose by 50% in the elderly and patients with renal failure.
- When changing the route of administration, it is suggested that the morphine equianalgesic dose first be determined prior to calculating the new dose (oral to intravenous morphine conversion is 3:1, oral to subcutaneous morphine conversion is 2:1).

Step 4: If pain is controlled, start at 50-75% of the equianalgesic dose; if the pain is uncontrolled than start at 100% of the dose.
Step 5: Determine the appropriate intervals of administration and amount per dose.
Step 6: Provide appropriate rescue dosing for breakthrough pain.
Step 7: Titrate baseline and as needed doses to provide effective pain relief.
Step 8: Cathartic and stool-softening medications should be started with the initiation of opioids.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American Pain Society: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[33]	• Before initiating chronic opioid therapy, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction. • When starting chronic opioid therapy, informed consent should be obtained. A continuing discussion with the patient regarding chronic opioid therapy should include goals, expectations, potential risks, and alternatives to chronic opioid therapy. • Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids,

Clinical Guideline	Recommendations
	attainment of therapeutic goals, and predicted or observed harms. • In patients on chronic opioid therapy who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. • Clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist. • In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the treatment plan on an ongoing basis, and consider more frequent follow-up visits. • Clinicians should taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects. • In patients on around-the-clock chronic opioid therapy with breakthrough pain, clinicians may consider as needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk. • Clinicians should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Clinicians should encourage minimal or no use of opioids during pregnancy, unless potential benefits outweigh risks. If chronic opioid therapy is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn.
American College of Rheumatology Subcommittee on Osteoarthritis: **Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee (2000)**[34]	• The goals of management of patients with osteoarthritis include control of pain and improvement in function and health-related quality of life, with avoidance of toxic effects of therapy. • Drug therapy for pain management is most effective when combined with nonpharmacologic strategies, therefore nonpharmalogical therapies should be maintained throughout treatment. <u>Nonpharmacological Therapy</u> • Patient and family/caregiver education, participation in self-management programs and personalized social support are recommended to improve outcomes. • Physical therapy and occupational therapy play central roles in the management of patients with functional limitations. • Quadricep strengthening and aerobic exercise are recommended for patients with knee osteoarthritis. • Weight loss is recommended in patients with knee and hip osteoarthritis. • Assistive devices for ambulation, patellar taping, appropriate footwear, bracing and assistive devices may help improve mobility and activities of daily living. <u>Pharmacological Therapy</u> • Relief of mild-to-moderate joint pain afforded by the simple analgesic, acetaminophen (APAP), is comparable with that achievable with a nonsteroidal anti-inflammatory drugs (NSAIDs).

Clinical Guideline	Recommendations
	• In individuals with osteoarthritis of the knee who have mild-to-moderate pain, do not respond to APAP, and do not wish to take systemic therapy, the use of topical analgesics (e.g., methyl salicylate or capsaicin cream) is appropriate as either adjunctive treatment or monotherapy. • The options for medical management of osteoarthritis that has not responded to APAP or topical agents in patients who are at increased risk for a serious upper gastrointestinal adverse event, such as bleeding, perforation, or obstruction, include cyclooxygenase (COX)-2 inhibitors, a nonselective NSAID plus misoprostol or a proton pump inhibitor, non-acetylated salicylate , or local intraarticular therapy. • Celecoxib has been found to be more effective than placebo and comparable in efficacy with naproxen in patients with hip or knee osteoarthritis. • Of further advantage with respect to upper gastrointestinal bleeding, neither of the COX-2-specific inhibitors has a clinically significant effect on platelet aggregation nor bleeding time. • Coxibs are an alternative to nonselective NSAIDs in patients at risk of developing gastrointestinal toxicity associated with NSAID therapy. • Additionally, at doses recommended for treatment of osteoarthritis, both celecoxib and rofecoxib appear to be better tolerated, with a lower incidence of dyspepsia and other gastrointestinal side effects, than comparator nonselective NSAIDs. • Tramadol, a centrally acting opioid agonist, can be considered for use in patients who have contraindications to COX-2-specific inhibitors and nonselective NSAIDs, including impaired renal function or in patients who have not responded to previous oral therapy. • More potent opioid therapy can be considered in patients who do not respond to or cannot tolerate tramadol and who continue to have severe pain. • It is reasonable to use the recommended agents in combination. However, only a single NSAID should be used at any given time, the sole exception being the concomitant use of a cardioprotective dose of aspirin (81-325 mg/day) with other NSAIDs.
American Academy of Orthopedic Surgeons (AAOS): **Clinical Practice Guideline on Osteoarthritis of the Knee (2008)**[35]	Nonpharmacological/Surgical Therapy • Patients with symptomatic osteoarthritis of the knee should be encouraged to participate in self-management educational programs, lose and maintain weight loss if overweight (body mass index >25), participate in low-impact aerobic fitness exercises and use range of motion/flexibility exercises and quadriceps strengthening. • Patients with symptomatic osteoarthritis of the knee should use patellar taping for short term relief of pain and improvement in function. Lateral heel wedges should not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee. • Needle lavage and arthroscopy with debridement or lavage should not be used for patients with primary symptomatic osteoarthritis of the knee. Arthroscopic partial meniscectomy or loose body removal is an option in patients with symptomatic osteoarthritis of the knee who also have primary signs and symptoms of a torn meniscus and/or a loose body. Pharmacological Therapy • Glucosamine and/or chondroitin sulfate should not be prescribed for

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>patients with symptomatic osteoarthritis of the knee.
• Patients with symptomatic osteoarthritis of the knee should receive one of the following analgesics for pain unless there are contraindications to this treatment:
○ APAP (not to exceed 4 grams per day)
○ NSAIDs
• Patients with symptomatic osteoarthritis of the knee and increased gastrointestinal risk (age ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of gastrointestinal bleeding, concurrent corticosteroids and/or concomitant use of anticoagulants) should receive one of the following analgesics for pain:
○ APAP (not to exceed 4 grams per day)
○ Topical NSAIDs
○ Nonselective oral NSAIDs plus gastro-protective agent
○ COX-2 inhibitors
• Intra-articular corticosteroids can be used for short-term pain relief for patients with symptomatic osteoarthritis of the knee.</td></tr>
<tr><td>Treatment Guidelines from The Medical Letter: Drugs for Pain (2007)[36]</td><td>• Aspirin, APAP, and NSAIDS are recommended as first line agents for mild to moderate pain.
• For moderate pain, NSAIDS have been shown to be more effective than aspirin and APAP, and may be equal to or greater than APAP/opioid combination products or opioids administered via injection, at recommended doses.
• Strong opioid full agonists are recommended as the first line treatment for severe pain.
• Full opioid agonists generally have no ceiling effect and the dose may be increased as tolerated based on adverse effects.
• Patients who do not respond to one opioid may respond to another. The choice of opioid should be based on adequate analgesia being provided with minimal adverse effects.
• When frequent as-needed dosing with short–acting agents becomes inappropriate, use of long-acting agents is warranted.
• Combination regimens, including opioids, non-opioids, and adjuvant analgesics, are useful for severe chronic pain.</td></tr>
<tr><td>American College of Physicians (ACP): Guidelines for the Diagnosis and Treatment of Low Back Pain (LBP) (2007)[37]</td><td>• Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work), and duration of symptoms.
• The potential interventions for lower back pain are outlined below:
Interventions for the Management of LBP
<table><tr><th>Intervention type</th><th>Acute pain (duration < 4 weeks)</th><th>Subacute or chronic pain (duration > 4 weeks)</th></tr><tr><td>Self-care</td><td></td><td></td></tr><tr><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr><tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr><tr><td>Books, handouts</td><td>Yes</td><td>Yes</td></tr><tr><td>Pharmacologic therapy</td><td></td><td></td></tr><tr><td>APAP</td><td>Yes</td><td>Yes</td></tr><tr><td>Tricyclic antidepressants</td><td>No</td><td>Yes</td></tr><tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr></table></td></tr>
</table>

Clinical Guideline	Recommendations
	NSAIDs: Yes / Yes Skeletal muscle relaxants: Yes / No **Tramadol, opioids: Yes / Yes** Nonpharmacologic therapy Acupuncture: No / Yes Cognitive behavior therapy: No / Yes Exercise therapy: No / Yes Massage: No / Yes Progressive relaxation: No / Yes Spinal manipulation: Yes / Yes Yoga: No / Yes Intensive interdisciplinary rehabilitation: No / Yes Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482. • Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors. • In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, APAP or NSAIDs are the first-line options. • APAP is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen. • Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with APAP or NSAIDs. Evidence is insufficient to recommend one opioid over another.
A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: **Diagnosis and Treatment of LBP (2007)**[38]	• Clinicians should consider the use of medications with proven benefits in conjunction with self-care. • Clinicians should assess the severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy. • For most patients, first-line medical options are APAP or NSAIDs. • Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution.

Clinical Guideline	Recommendations
	• Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
British Society for Rheumatology and British Health Professionals in Rheumatology: **Guideline for the Management of Gout (2007)**[39]	Management of Acute Gout • After an acute gout episode, affected joints should be rested and analgesic and anti-inflammatory drug therapy should be commenced immediately and continued for 1 to 2 weeks. • Fast-acting oral NSAIDs at maximum doses are the drugs of choice in gout when there are no contraindications. • Physicians should follow standard guidelines for the use of NSAIDs and COX-2 inhibitors in patients with increased risk of peptic ulcers, bleeds or perforations. • Colchicine can be an effective alternative but it has a slower onset of action than NSAID therapy. • Allopurinol should not be commenced during an acute attack. It should be continued if used when an acute attack occurs and the acute attack should be treated conventionally. • Opiate analgesics can be used as adjunct therapy. • Intra-articular corticosteroids are highly effective in acute gouty mono-arthritis and can be effective in patients unable to tolerate NSAIDs or in patient's refractory to other treatments. Diet, Lifestyle Modification and Non-pharmacological Therapy • In overweight patients, dietary modification should be attempted to achieve ideal body weight. However, "crash dieting" and high protein/low carbohydrate diets should be avoided. Patients should be instructed on proper diet to avoid precipitation of an acute gout attack. • Affected joints should be elevated and exposed in a cool environment. • Moderate physical exercise should be encouraged. Management of Recurrent, Intercritical and Chronic Gout • The plasma urate should be maintained below 300 µmol/L. • Uric acid lowering drug therapy should be started if further attacks occur within 1 year and should also be offered to patients with tophi, renal insufficiency, uric acid stones and to patients who need to continue treatment with diuretics. • Uric acid-lowering drug therapy should be delayed until 1 to 2 weeks after inflammation has settled. • Long-term treatment of recurrent uncomplicated gout should be initiated with allopurinol at a starting dose of 50 to 100 mg daily and increasing by 50 to 100 mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (plasma urate <300 µmol/L) or maximum dose (900 mg daily) is reached. • Uricosuric agents can be used as second-line drugs in patients who excrete sufficient uric acid in those resistant to, or intolerant of, allopurinol. Preferred drugs include: sulphinpyrazone in patients with normal renal function or benzbromarone in patients with mild to moderate renal insufficiency. • Colchicine should be co-prescribed following initiation of treatment with allopurinol or uricosuric drugs, and continued for up to 6 months. An NSAID or COX-2 inhibitor can be substituted if colchicine cannot be used (provided that there are no contraindications). However, the

Clinical Guideline	Recommendations
	duration of therapy should be limited to 6 weeks. • Aspirin in low doses (75 to 150 mg daily) has insignificant effects on the plasma urate and can be used; however, aspirin in analgesic doses (600 to 2,400 mg daily) interferes with uric acid excretion and should be avoided.
American Society of Pain Educators: **Treatment Guidelines for Diabetic Peripheral Neuropathic Pain (2006)**[40]	• For the treatment of diabetic peripheral neuropathic pain, first line agents, including duloxetine, controlled release oxycodone, pregabalin, and tri-cyclic antidepressants (TCAs), should be titrated to maximum tolerated doses. • If no improvement is seen within 3 weeks of initiating therapy, second line agents may be considered (carbamazepine, gabapentin, lamotrigine, tramadol, and extended release venlafaxine). • Other recommended agents include topical capsaicin, topical lidocaine, bupropion, citalopram, methadone, paroxetine, phenytoin, and topiramate.
European Federation of Neurological Societies: **Guidelines on Pharmacological Treatment of Neuropathic Pain (2006)**[41]	<u>Painful Polyneuropathy</u> • Treatments with established efficacy include TCAs, duloxetine, venlafaxine, gabapentin, pregabalin, opioids and tramadol. • A TCA, gabapentin or pregabalin are considered first line agents. • Duloxetine and venlafaxine are considered second line agents. • Duloxetine and venlafaxine have moderate efficacy, but are safer and have less contraindications than TCAs and should be preferred to TCAs in patients with cardiovascular risk factors. • Other second/third-line agents include opioids and lamotrigine. <u>Postherpetic Neuralgia</u> • Treatments with established efficacy include TCAs, gabapentin, pregabalin and opioids. • A TCA, gabapentin or pregabalin are considered first line agents. • Topical lidocaine may be an option in elderly patients, particularly in patients with allodynia and a small area of pain. • Opioids should be considered a second line agent. <u>Trigeminal Neuralgia</u> • Carbamazepine and oxcarbazepine are considered first line agents. • There is no evidence that combination therapies are advantageous. <u>Central Pain</u> • Treatment may be based on general principles for peripheral neuropathic pain treatment and for side-effect profile. • A trial with other drugs found effective on other central pain conditions is the recommended treatment.
Canadian Pain Society: **Pharmacological Management of Chronic Neuropathic Pain- Consensus Statement and Guidelines (2007)**[42]	• First-line treatments consist of certain antidepressants (TCAs) and anticonvulsants (gabapentin and pregabalin). • Second-line treatments consist of serotonin/noradrenaline reuptake inhibitors and topical lidocaine. • Third-line treatments consist of tramadol and controlled-release opioids. • Fourth-line treatments consist of cannabinoids, methadone and anticonvulsants with lesser evidence of efficacy, such as lamotrigine, topiramate and valproic acid. • Treatment must be individualized for each patient based on efficacy, side-effect profile and drug accessibility, which includes cost.

Clinical Guideline	Recommendations
European League Against Rheumatism (EULAR): **Evidence-Based Recommendations for the Management of Fibromyalgia Syndrome (2008)**[43]	• Tramadol is recommended for the management of pain in fibromyalgia. • Simple analgesics such as APAP and other weak opioids can be considered in the treatment of fibromyalgia. Corticosteroids and strong opioids are not recommended. • Antidepressants such as amitriptyline, fluoxetine, duloxetine and pregabalin reduce pain and should be considered for the treatment of fibromyalgia.

Conclusions

Opioids (narcotics) have been the mainstay of pain treatment for a number of years with short acting narcotic agents playing an important role in the treatment of acute pain and breakthrough pain in patients with chronic pain. Clinical trials have shown their efficacy in treating pain due to a number of etiologies. However, no one short acting narcotic has continuously proven to be more effective than another when given at equipotent doses. Combination products consisting of an opioid and a non-opioid allow doses of the opioid agent to remain low, side effects to be minimized, and additive analgesic effects maximized.

The short acting narcotics are similar in their documented adverse events as the adverse events tend to be class effects rather than effects of a specific agent. Many of these adverse effects subside with continued dosing as tolerance is built.

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Nonpreferred short-acting narcotics require prior authorization with the following approval criteria:

- The member has had a documented side effect, allergy, or treatment failure to at least two medications not requiring prior approval. (If a product has an AB rated generic, one trial must be the generic.)

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